## Online supplementary appendix: Exploring the effects of BCG vaccination in patients diagnosed with tuberculosis: observational study using the Enhanced Tuberculosis Surveillance system

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**Model output: All-cause mortality**

**Supplementary table S1:** Summary of logistic regression model output with BCG vaccination as the exposure and all-cause mortality as the outcome.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable | Total | All-cause mortality | Univariable | | Multivariable | |
| OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Total cases | 25993 | 807 (3) |  |  |  |  |
| BCG vaccination |  |  |  | <0.001 |  | 0.001 |
| No | 7620 | 473 (6) | 1 |  | 1 |  |
| Yes | 18373 | 334 (2) | 0.28 (0.24 to 0.32) |  | 0.76 (0.64 to 0.89) |  |
| Age |  |  |  | <0.001 |  | <0.001 |
| Sex |  |  |  | <0.001 |  | <0.001 |
| Female | 11502 | 296 (3) | 1 |  | 1 |  |
| Male | 14491 | 511 (4) | 1.45 (1.34 to 1.58) |  | 1.48 (1.26 to 1.73) |  |
| IMD rank (with 1 as most deprived and 5 as least deprived) |  |  |  | <0.001 |  | 0.001 |
| 1 | 9891 | 298 (3) | 1 |  | 1 |  |
| 2 | 8136 | 219 (3) | 0.85 (0.76 to 0.95) |  | 0.86 (0.70 to 1.04) |  |
| 3 | 4100 | 120 (3) | 1.06 (0.93 to 1.20) |  | 0.66 (0.52 to 0.84) |  |
| 4 | 2341 | 98 (4) | 1.47 (1.28 to 1.70) |  | 0.72 (0.55 to 0.93) |  |
| 5 | 1525 | 72 (5) | 1.70 (1.45 to 1.99) |  | 0.64 (0.47 to 0.85) |  |
| UK birth status |  |  |  | <0.001 |  | 0.136 |
| Non-UK Born | 19115 | 442 (2) | 1 |  | 1 |  |
| UK Born | 6878 | 365 (5) | 2.62 (2.40 to 2.85) |  | 1.25 (0.93 to 1.67) |  |
| Ethnic group |  |  |  | <0.001 |  | 0.171 |
| White | 4699 | 380 (8) | 1 |  | 1 |  |
| Black-Caribbean | 634 | 25 (4) | 0.45 (0.35 to 0.58) |  | 0.95 (0.59 to 1.53) |  |
| Black-African | 4681 | 62 (1) | 0.14 (0.12 to 0.17) |  | 0.87 (0.59 to 1.29) |  |
| Black-Other | 247 | 2 (1) | 0.13 (0.06 to 0.26) |  | 0.40 (0.10 to 1.69) |  |
| Indian | 7041 | 168 (2) | 0.28 (0.25 to 0.31) |  | 0.80 (0.58 to 1.10) |  |
| Pakistani | 4067 | 103 (3) | 0.30 (0.27 to 0.34) |  | 0.65 (0.46 to 0.92) |  |
| Bangladeshi | 1079 | 18 (2) | 0.21 (0.16 to 0.27) |  | 0.69 (0.40 to 1.22) |  |
| Chinese | 286 | 7 (2) | 0.34 (0.23 to 0.51) |  | 0.69 (0.30 to 1.62) |  |
| Mixed / Other | 3259 | 42 (1) | 0.16 (0.13 to 0.19) |  | 0.59 (0.39 to 0.91) |  |
| Calendar year |  |  | 1.06 (1.04 to 1.08) | <0.001 | 1.10 (1.05 to 1.15) | <0.001 |
| OR (95% CI): unadjusted odds ratio with 95% confidence intervals,  aOR (95% CI): adjusted odds ratios with 95% confidence intervals | | | | | | |

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**Secondary exposure: Age at vaccination**

We calculated age at vaccination as year of vaccination minus year of birth. We categorized age at vaccination into to , to , to and 16+ years because the distribution was bi-model with modes at 0 and 12 years. This categorization captures the current UK policy of vaccination at birth, historic policy of vaccination at 13-15 years and catch up vaccination for high risk children.

**Supplementary table S2:** Summary of associations between age at vaccination and all outcomes in individuals who were vaccinated - the baseline exposure is vaccination at birth compared to vaccination from 1 to < 12, 12 to < 16, and 16+ years of age. Cases represents all notifications with complete data and a given BCG status, regardless of outcome. Cases with outcome is similarly defined but includes only cases with the specified outcome.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Age at BCG | Univariable | | | | Multivariable | | | |
| Cases\* | Cases with outcome (%) | OR (95% CI) | P-value | Cases† | Cases with outcome (%) | aOR (95% CI) | P-value |
| All-cause mortality | < 1 | 5234 | 45 (1) | 1 | <0.001 | 4626 | 43 (1) | 1 | 0.127 |
| 1 to < 12 | 1915 | 58 (3) | 3.60 (2.43 to 5.34) |  | 1678 | 52 (3) | 1.36 (0.85 to 2.16) |  |
|  | 12 to < 16 | 1267 | 41 (3) | 3.86 (2.51 to 5.91) |  | 1094 | 32 (3) | 0.81 (0.45 to 1.46) |  |
|  | ≥ 16 | 408 | 27 (7) | 8.17 (5.01 to 13.32) |  | 327 | 25 (8) | 1.41 (0.76 to 2.63) |  |
| Death due to TB (in those who died‡) | < 1 | 27 | 20 (74) | 1 | 0.118 | 27 | 20 (74) | 1 | 0.543 |
| 1 to < 12 | 43 | 20 (47) | 0.30 (0.11 to 0.87) |  | 39 | 18 (46) | 0.36 (0.08 to 1.51) |  |
| 12 to < 16 | 23 | 13 (57) | 0.46 (0.14 to 1.50) |  | 17 | 9 (53) | 0.40 (0.06 to 2.52) |  |
|  | ≥ 16 | 17 | 8 (47) | 0.31 (0.09 to 1.12) |  | 17 | 8 (47) | 0.35 (0.06 to 2.16) |  |
| Recurrent TB | < 1 | 5909 | 284 (5) | 1 | 0.463 | 5275 | 258 (5) | 1 | 0.246 |
| 1 to < 12 | 2174 | 105 (5) | 1.01 (0.80 to 1.26) |  | 1928 | 92 (5) | 0.84 (0.65 to 1.09) |  |
|  | 12 to < 16 | 1421 | 58 (4) | 0.84 (0.63 to 1.12) |  | 1242 | 51 (4) | 0.70 (0.48 to 1.02) |  |
|  | ≥ 16 | 448 | 26 (6) | 1.22 (0.81 to 1.85) |  | 362 | 19 (5) | 0.82 (0.49 to 1.37) |  |
| Pulmonary TB | < 1 | 5946 | 2828 (48) | 1 | <0.001 | 5305 | 2510 (47) | 1 | 0.005 |
| 1 to < 12 | 2194 | 1159 (53) | 1.23 (1.12 to 1.36) |  | 1941 | 1033 (53) | 1.15 (1.02 to 1.29) |  |
|  | 12 to < 16 | 1425 | 971 (68) | 2.36 (2.09 to 2.67) |  | 1245 | 846 (68) | 1.09 (0.92 to 1.29) |  |
|  | ≥ 16 | 453 | 279 (62) | 1.77 (1.45 to 2.15) |  | 364 | 225 (62) | 1.47 (1.15 to 1.88) |  |
| Sputum smear status - positive | < 1 | 1753 | 836 (48) | 1 | <0.001 | 1557 | 742 (48) | 1 | 0.862 |
| 1 to < 12 | 755 | 394 (52) | 1.20 (1.01 to 1.42) |  | 682 | 348 (51) | 0.96 (0.79 to 1.17) |  |
| 12 to < 16 | 556 | 357 (64) | 1.97 (1.62 to 2.40) |  | 486 | 308 (63) | 1.06 (0.81 to 1.39) |  |
|  | ≥ 16 | 157 | 84 (54) | 1.26 (0.91 to 1.75) |  | 131 | 68 (52) | 0.93 (0.63 to 1.37) |  |
| OR (95% CI): unadjusted odds ratio with 95% confidence intervals,  aOR (95% CI): adjusted odds ratios with 95% confidence intervals,  \* Univariable sample size for outcomes ordered as in table (% of vaccinated cases) = 8824 (36%), 110 (28%), 9952 (41%), 10018 (41%), 3221 (13%),  † Multivariable sample size with outcomes ordered as in table (% of vaccinated cases) = 7725 (32%), 100 (25%), 8807 (36%), 8855 (36%), 2856 (12%)  ‡ Death due to TB in those who died and where cause of death was known | | | | | | | | | |

**Sensitivity analysis of the missing data using multiple imputation**

We found that repeating the analysis with an imputed data set had some effect on the results from the complete case analysis. There was a decrease in the accuracy of effect size estimates for BCG vaccination, some increase in p-values (supplementary table S5). However, none of the estimated effects changed their direction, and there were no detectable systematic changes in the results.

For the secondary exposure variables (years since vaccination and age at vaccination, (supplementary table S6 and supplementary table S7), we found a change in direction of the point estimate between years since vaccination and all-cause mortality and recurrent TB, but similar results for age at vaccination and outcomes.

**Supplementary table S3:** Summary of associations between BCG vaccination and all outcomes, using pooled imputed data.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Univariable | | | Multivariable | | |
| OR (95% CI) | P-value | fmi | aOR (95% CI) | P-value | fmi |
| All-cause mortality | 0.44 (0.35 to 0.56) | <0.001 | 90 | 0.76 (0.61 to 0.94) | 0.013 | 85 |
| Death due to TB (in those who died\*) | 0.94 (0.57 to 1.56) | 0.810 | 85 | 0.89 (0.52 to 1.51) | 0.651 | 85 |
| Recurrent TB | 0.83 (0.75 to 0.92) | <0.001 | 56 | 0.90 (0.81 to 1.00) | 0.058 | 54 |
| Pulmonary TB | 0.84 (0.79 to 0.90) | <0.001 | 70 | 0.99 (0.93 to 1.06) | 0.814 | 62 |
| Sputum smear status - positive | 0.88 (0.82 to 0.94) | <0.001 | 65 | 1.01 (0.94 to 1.08) | 0.886 | 60 |
| OR: odds ratio with 95% confidence intervals,  aOR: adjusted odds ratio with 95% confidence intervals,  fmi: fraction of missing information,  \* Death due to TB in those who died and where cause of death was known | | | | | | |

**Supplementary table S4:** Summary of associations between years since vaccination and all outcomes, using pooled imputed data. There was insufficient data to estimate an effect for deaths due to TB (in those who died)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Univariable | | | Multivariable | | |
| OR (95% CI) | P-value | fmi | aOR (95% CI) | P-value | fmi |
| All-cause mortality | 3.28 (1.85 to 5.79) | <0.001 | 50 | 12.19 (3.48 to 42.64) | <0.001 | 70 |
| Death due to TB (in those who died\*) | *Insufficient data* | - | 0 | *Insufficient data* | - | 0 |
| Recurrent TB | 1.29 (1.00 to 1.66) | 0.050 | 39 | 0.81 (0.59 to 1.11) | 0.187 | 44 |
| Pulmonary TB | 0.58 (0.52 to 0.66) | <0.001 | 33 | 0.99 (0.84 to 1.17) | 0.913 | 40 |
| Sputum smear status - positive | 0.99 (0.82 to 1.19) | 0.891 | 70 | 0.95 (0.77 to 1.18) | 0.648 | 60 |
| OR: odds ratio with 95% confidence intervals,  aOR: adjusted odds ratio with 95% confidence intervals,  fmi: fraction of missing information,  \* Death due to TB in those who died and where cause of death was known | | | | | | |

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**Supplementary table S5:** Summary of associations between age at vaccination and all outcomes, using pooled imputed data (reference is vaccination at <1 year).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Age group (years) | Univariable | | | Multivariable | | |
| OR (95% CI) | P-value | fmi | aOR (95% CI) | P-value | fmi |
| All-cause mortality | 1 to < 12 | 6.48 (4.71 to 8.91) | <0.001 | 70 | 1.69 (1.18 to 2.40) | 0.004 | 68 |
|  | 12 to < 16 | 3.33 (2.50 to 4.43) | <0.001 | 78 | 1.57 (1.13 to 2.19) | 0.008 | 79 |
|  | ≥ 16 | 3.36 (2.56 to 4.41) | <0.001 | 69 | 1.01 (0.70 to 1.46) | 0.948 | 71 |
| Death due to TB (in those who died\*) | 1 to < 12 | 0.45 (0.22 to 0.92) | 0.028 | 62 | 0.47 (0.21 to 1.04) | 0.063 | 62 |
|  | 12 to < 16 | 0.41 (0.22 to 0.75) | 0.004 | 67 | 0.40 (0.20 to 0.78) | 0.008 | 67 |
|  | ≥ 16 | 0.53 (0.28 to 1.00) | 0.051 | 54 | 0.47 (0.20 to 1.12) | 0.088 | 62 |
| Recurrent TB | 1 to < 12 | 1.39 (1.11 to 1.73) | 0.004 | 41 | 1.04 (0.82 to 1.32) | 0.736 | 41 |
|  | 12 to < 16 | 1.01 (0.88 to 1.16) | 0.892 | 45 | 0.86 (0.75 to 1.00) | 0.052 | 44 |
|  | ≥ 16 | 0.95 (0.79 to 1.15) | 0.598 | 53 | 0.77 (0.61 to 0.98) | 0.034 | 55 |
| Pulmonary TB | 1 to < 12 | 1.83 (1.59 to 2.10) | <0.001 | 46 | 1.36 (1.17 to 1.58) | <0.001 | 44 |
|  | 12 to < 16 | 1.28 (1.19 to 1.36) | <0.001 | 35 | 1.12 (1.04 to 1.21) | 0.002 | 36 |
|  | ≥ 16 | 2.28 (2.10 to 2.48) | <0.001 | 34 | 1.10 (0.98 to 1.23) | 0.107 | 40 |
| Sputum smear status - positive | 1 to < 12 | 1.49 (1.21 to 1.84) | <0.001 | 74 | 1.08 (0.85 to 1.37) | 0.549 | 76 |
|  | 12 to < 16 | 1.29 (1.17 to 1.43) | <0.001 | 65 | 1.09 (0.97 to 1.22) | 0.158 | 67 |
|  | ≥ 16 | 2.40 (2.16 to 2.66) | <0.001 | 58 | 1.20 (1.04 to 1.37) | 0.011 | 59 |
| OR: odds ratio with 95% confidence intervals,  aOR: adjusted odds ratio with 95% confidence intervals,  fmi: fraction of missing information,  \* Death due to TB in those who died and where cause of death was known | | | | | | | |

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**Sensitivity analysis of the study population**

**Supplementary table S6:** Summary of associations between BCG vaccination and all outcomes; cases that have no recurrent flag in the ETS (n=50407), and cases that would have been eligible for the BCG schools scheme (n=9943). Those defined to be eligible for the schools scheme are the UK born, that were aged 14 or over in 2004

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study population | Outcome | BCG | Univariable | | Multivariable | |
| OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Recurrent cases dropped |  |  |  |  |  |  |
| All-cause mortality | No | 1 | <0.001 | 1 | <0.001 |
|  | Yes | 0.27 (0.23 to 0.31) |  | 0.73 (0.61 to 0.86) |  |
|  | Death due to TB (in those who died\*) | No | 1 | 0.709 | 1 | 0.147 |
|  | Yes | 0.94 (0.68 to 1.31) |  | 0.74 (0.49 to 1.11) |  |
|  | Recurrent TB | No | 1 | <0.001 | 1 | <0.001 |
|  |  | Yes | 0.61 (0.55 to 0.69) |  | 0.76 (0.66 to 0.87) |  |
|  | Pulmonary TB | No | 1 | <0.001 | 1 | 0.672 |
|  | Yes | 0.83 (0.79 to 0.87) |  | 0.99 (0.93 to 1.04) |  |
|  | Sputum smear status - positive | No | 1 | 0.141 | 1 | 0.871 |
|  | Yes | 0.94 (0.88 to 1.02) |  | 1.01 (0.92 to 1.10) |  |
| Cases eligible for the  schools scheme |  |  |  |  |  |  |
|  |  |  |  |  |  |
| All-cause mortality | No | 1 | <0.001 | 1 | 0.018 |
|  | Yes | 0.24 (0.19 to 0.29) |  | 0.72 (0.55 to 0.95) |  |
|  | Death due to TB (in those who died\*) | No | 1 | 0.893 | 1 | 0.987 |
|  | Yes | 0.96 (0.57 to 1.63) |  | 0.99 (0.49 to 2.03) |  |
|  | Recurrent TB | No | 1 | <0.001 | 1 | <0.001 |
|  | Yes | 0.51 (0.42 to 0.61) |  | 0.66 (0.52 to 0.84) |  |
|  | Pulmonary TB | No | 1 | 0.017 | 1 | 0.417 |
|  | Yes | 0.87 (0.78 to 0.98) |  | 0.94 (0.82 to 1.08) |  |
|  | Sputum smear status - positive | No | 1 | 0.613 | 1 | 0.588 |
|  | Yes | 1.04 (0.89 to 1.22) |  | 1.05 (0.87 to 1.27) |  |
| OR: odds ratio with 95% confidence intervals,  aOR: adjusted odds ratio with 95% confidence intervals,  \* Death due to TB in those who died and where cause of death was known | | | | | | |